Draft NTP Research Concept: Silica Flour

Project Leader:
Helen C. Cunny, DIR/NTP/Program Operations Branch

Nomination Background and Rationale:
Silica flour is finely ground or powdered crystalline silicon dioxide (micronized α-quartz, CAS No. 14808-60-7) with a particle size from 1 to 100 μm. Silica flour was nominated by a private individual for toxicological testing via dermal and oral routes of exposure. The nomination is based on evidence that occupational exposure to silica is linked to higher rates of occurrence of autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and scleroderma. Past studies of the effects of silica on biological systems have almost exclusively been via inhalation or instillation, and exposure to respirable crystalline silica is known to be carcinogenic (1). The nominator postulated that there could be hazard concerns related to silica exposure through oral or dermal routes, particularly immunotoxicity.

Finely ground crystalline silica, or silica flour is used industrially as an abrasive cleaner and as a filler. Silica flour is found in scouring powder and metal polish. It is an extender in paint, a wood filler, and a component in road surfacing mixtures. It is also used in some foundry processes and in glass, ceramic, porcelain, tile and clay production. Finely ground quartz crystals are used in some skin-care products, including exfoliants, scar and acne treatments, and corn, callus, and wart removers; mineral-based cosmetics; and hair- and nail-care products (2). The nominator for silica flour suggested that it might be used as a filler in OTC pharmaceuticals such as vitamins or pain relievers, but this has not been confirmed by NTP.

The actual number of workers industrially exposed to silica flour is unknown. However, it is estimated that approximately 2 million workers are exposed to silica when all dusty occupations and particle size ranges are considered. There is also potential exposure to the general population through use of the commercial products listed above.

Numerous studies have investigated the effect of silica on the immune system, most all using non-oral routes of exposure. Silica has long been known to have an adjuvant effect on antibody production (3). Although the mechanism by which silica acts as an adjuvant is not fully understood, it appears to be related to the release of inflammatory mediators as the immune system attempts to eliminate the silica particles. Macrophages respond to internalized silica by up-regulating cytokine production (including interleukin (IL)-1 and tumor necrosis factor (TNF), which stimulate other cells and enhance the inflammatory response. Silica can also cause cell death by apoptosis. These effects are consistent with observed pathologic features of SLE (eg, inflammation, altered apoptosis) (4).

Key Issues:
Before conducting studies to investigate immunotoxicity of oral or dermal exposure to silica flour, consideration must be given to (1) the test material chosen for study, and (2)

the bioavailability of silica flour after oral or dermal exposure. There are a variety of grades of silica flour based on mean particle size or mesh grade. In addition, the micromorphology and surface features of the silica particles may play a role in the biological responses directed toward them. The rod-like shape of crystallites has been reported to enhance the cytotoxicity of silica toward macrophages (5).

A second key issue to be addressed concerns the disposition of silica upon oral or dermal exposure. Although the nominator initially suggested dermal exposure, only slight if any dermal absorption would be expected due to its insolubility. Therefore, the oral route of exposure is recommended as the first route for testing.

Another key issue concerns the paucity of oral toxicology data on silica flour reported in the literature. Because of this data gap, general toxicity and carcinogenicity studies should be considered. However, these might be ranked as a lower priority compared to immunotoxicity studies because of the available data on inhalation toxicity of crystalline silica. Concomitant with inhalation exposure, there is always some oral exposure when particles deposited in the nasopharynx are cleared by mucocilary transport and swallowed.

Proposed Approach:
Currently, no information has been located to indicate particle size or shape for silica flour that is predominant in commercial products and/or non-inhalation exposure situations. Therefore, this is one key preliminary issue to be resolved. If no information can be found, a silica flour with a strict particle size range of 1-2 um would be tested as it might be predicted that a smaller particle has a greater chance of being absorbed. Depending on availability of analytical methodology, the feasibility of conducting an ADME study should be explored to determine the disposition of silica flour after oral dosing. Based on the particulate characteristics of silica flour found to be used in commercial products, more than one particle size/shape might be chosen for ADME studies to determine which (if any) particle persists within certain tissues or interacts with macrophages or other components of the immune system after exposure.

If it is found through the ADME studies that silica flour is bioavailable after oral dosing, immunotoxicity screening should be conducted using the NTP tiered testing panel to investigate the tissues and processes that may be targeted by silica following oral administration. If the compound is shown to be immunologically active via this route of exposure, further studies using appropriate models such as mrl/lpr or NZM mice for clinically relevant autoimmune diseases will be conducted.

Specific Aims:
1. Obtain more information on potential human exposure to silica flour through oral or dermal exposure. Determine silica flour content and particle characteristics of the various products marketed containing silica flour.

2. Define the appropriate test material for investigation in laboratory animals. Examine the feasibility of producing/obtaining test material in well-defined and homogeneous size ranges.

3. Conduct ADME studies (primarily distribution) following oral administration to determine bioavailability and presence in tissues. If feasible, perform immunotoxicity screens during these studies.

4. If particles with different sizes/surface characteristics are used, determine if there is a particle size/shape factor involved in the bioavailability or immune response.

5. If silica is found to be available systemically, conduct immunology assay(s) to investigate specific effects on immune system components. Based on these results, choose a model system to investigate the development of autoimmune diseases such as lupus in the NZM mouse.

6. Based on findings above, consider conducting general toxicity studies using the oral route of exposure.

Significance and Expected Outcome:
Currently there is a paucity of information in the open literature on the potential toxicity of non-inhalation exposure to crystalline silica. These studies will investigate the potential for orally administered silica flour to affect the development of autoimmune diseases such as lupus in an animal model. Based on a tiered approach, general toxicity testing may also be conducted on silica flour using the oral route of exposure.

References:
(1) International Agency for Research on Cancer. Silica. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol 68: Silica and Some Silicates (1997).

(2) National Toxicology Program. Chemical Information Review Document for Silica Flour (Micronized α-Quartz) [CAS No. 14808-60-7] (2009).

(3) Pernis, B, Paronetto, F. Adjuvant effects of silica (tridymite) on antibody production. Proc Soc Exp Biol Med 110:390-392 (1962).

(4) Parks, CG, Conrad, K and Cooper, GS. Occupational exposure to crystalline silica and autoimmune disease. Environ Health Persp Suppl 107:5 (1999).

(5) Fenoglio, I, Fubini, B, Tiozzo, R, Di Renzo, F. Effect of micromorphology and surface reactivity of several unusual forms of crystalline silica on the toxicity to a monocyte-macrophage tumor cell line. Inhal Toxicol 12 (suppl 3):S81-9 (2000).